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Address for correspondence: Patrice Le Pape, Directeur EA1155-IICiMed, Université de Nantes, 1, rue Gaston Veil, BP 53508-44035 Nantes, France; email: patrice.le-pape@univ-nantes.fr

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Alexandre Alanio, Blandine Denis, Samia Hamane, Emmanuel Raffoux, Régis Peffault de Latour, Jean Menotti, Sandy Amorim, Sophie Touratier, Anne Bergeron, Stéphane Bretagne

Author affiliations: Groupe Hospitalier Saint-Louis-Lariboisière-Fernand-Widal, Assistance Publique-Hôpitaux de Paris, Paris, France (A. Alanio, B. Denis, S. Hamane, E. Raffoux, R. Peffault de Latour, J. Menotti, S. Amorim, S. Touratier, A. Bergeron, S. Bretagne); Université Paris Diderot, Sorbonne Paris Cité, Paris (A. Alanio, R. Peffault de Latour, J. Menotti, S. Amorim, A. Bergeron, S. Bretagne); National Reference Center of Invasive Mycoses and Antifungals, Institut Pasteur, Paris (A. Alanio, S. Bretagne); Le Centre National de la Recherche Scientifique URA 3012, Paris (A. Alanio, J. Menotti, S. Bretagne)

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To the Editor: First-line antifungal therapy for invasive aspergillosis (IA) is voriconazole, which is challenged by the emergence of azole resistance (*1*). A recent article reported a 3.2% prevalence of *Aspergillus fumigatus* isolates that are resistant to azole from 3,788 isolates screened in Europe (*2*). Of the 1,911 patients from whom the isolates were collected, IA developed in 10 (3 proven, 1 probable, 6 possible). Prevalence of azole-resistant *A. fumigatus* disease among patient populations at risk of IA was unavailable.

As described (*3*), we screened every *A. fumigatus* isolate recovered from respiratory specimens from patients with probable or proven IA in our hospital in Paris, France, during January 2012–December 2014. Every isolate recovered from 2% malt extract agar plates or Sabouraud dextrose agar slants (Bio-Rad, Marnes-la-Coquette, France) was incubated at 30°C and tested as individual isolates or multiple ones from a single sample by using itraconazole, voriconazole, and posaconazole Etest strips (bioMérieux, Marcy l'Etoile, France). Resistance was assessed for MICs >2.0 μg/μL for voriconazole and itraconazole and >0.25 μg/μL for posaconazole by using European Committee on Antimicrobial Susceptibility Testing clinical breakpoints for fungi (http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/AFST/Antifungal_breakpoints_v_7.0.pdf).

Every 4 months, a local multidisciplinary medical team classified each IA case by using the 2008 criteria established by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (*4*). For 148 patients (127 with hematologic malignancies and 21 with other conditions), the team recorded 152 episodes: 9 proven and 143 probable IA episodes. Possible IA was not analyzed because of a lack of microbiologic criteria. For 51 probable IA episodes, galactomannan positivity in blood or bronchoalveolar lavage fluid samples was the only microbiologic criterion used for classification. Cultures of respiratory samples (i.e., bronchoalveolar lavage fluid, tracheal aspirate, and sputum) or biopsies were positive for 99 episodes: 68 with *A. fumigatus* isolates and 31 with other *Aspergillus* spp. isolates. Among the 68 *A. fumigatus* isolates, 1 (1.5%) associated with probable IA was resistant to azoles (*5*). The isolate harbored the TR_{34}/L98H mutation (*5*), leading to a rate of IA caused by azole-resistant *A. fumigatus* of 0.7% (1/152) for total episodes recorded and 1% (1/99) for culture-positive episodes only. Nineteen (36%) of 53 culture-negative patients and 35 (37%) of 95 culture-positive patients died.

Azole resistance of *A. fumigatus* warrants specific surveillance in hospitals treating immunocompromised patients. Prevalence of resistant isolates can differ by hospital location and underlying disease (e.g., immunodeficiency vs. chronic lung diseases). When focusing on patients with probable or proven IA, we did not observe an emergence of azole-resistant *A. fumigatus* isolates during 2006–2009 (*3*) and 2012–2014 in France. Consequently, our center does not question the use of voriconazole as first-line treatment or of posaconazole as prophylaxis.

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Address for correspondence: Stéphane Bretagne, Laboratoire de Parasitologie-Mycologie, Hôpital Saint Louis, 1 rue Claude Vellefaux, 75010, Paris, France; email: stephane.bretagne@sls.aphp.fr

In Response:

Jan W.M. van der Linden, Maiken C. Arendrup, Willem J.G. Melchers, Paul E. Verweij

Author affiliations: Radboud University Medical Center, Nijmegen, the Netherlands (J.W.M. van der Linden, W.J.G. Melchers, P.E. Verweij); Statens Serum Institut, Copenhagen, Denmark (M.C. Arendrup)

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In Response: Alanio et al. comment that the prevalence of azole-resistant *Aspergillus* disease may differ, depending on location of the hospital where patients are admitted and the patients' underlying disease (*1*). Determining local or regional epidemiology, especially in areas where azole-resistant isolates are found in the environment, is indeed important. These isolates commonly harbor the TR_{34}/L98H or TR_{46}/Y121F/T289A resistance mechanism. Patients may inhale azole-resistant spores in the air and subsequently develop azole-resistant disease, even when they have never been treated with azoles (*2*). Although risk for inhalation of azole-resistant *Aspergillus* spores arguably might be similar for all patients, surveillance of *Aspergillus* isolates in the Netherlands indicates that resistance rates vary among hospitals. When all *A. fumigatus* isolates cultured from patients were investigated for azole resistance, resistance rates in the Netherlands ranged from 4.3% to 19.2% in 2013 and 3.8% to 13.3% in 2014 (*3*). The highest and lowest resistance rates were found in hospitals only 39 km from each other, supporting the observation made by Alanio et al. about variations in prevalence of azole-resistant *Aspergillus* disease (*1*).

More detailed surveillance is required to determine if local treatment guidelines should be reassessed. Two recent studies in the Netherlands investigated the risk of azole-resistant invasive aspergillosis in high-risk populations. One study conducted in a 33-bed tertiary-care university hospital intensive-care unit (ICU) showed that 26% of culture-positive patients with presumed invasive aspergillosis harbored azole-resistant isolates, a proportion 14% higher than that found in other departments in the hospital ($p = 0.06$) (*4*). The second study, which investigated azole resistance in the primary routine culture (including respiratory cultures) of 105 ICU and hematology patients, showed that the resistance rate (24.6%) for hematology patients was higher than the rate (4.5%) for ICU patients (*5*). Other countries have also reported higher prevalence of resistance in high-risk populations than in other populations.

One problem with assessing prevalence of azole resistance is that the recovery of *A. fumigatus* in culture may vary considerably among different patient groups. A recent audit in our hematology department over the past 5 years indicated that *A. fumigatus* was cultured in only 35% of patients who underwent bronchoalveolar lavage as part of a diagnostic work-up for pulmonary infection (P.E. Verweij, unpub. data). This outcome indicates that in culture-negative patients, presence of azole resistance will be missed.

In agreement with Alanio et al. (*1*), recent studies show a need to determine frequency of azole resistance at the hospital level and within different patient groups or departments. Although surveillance of unselected clinical cultures provides resistance rates at a national level and offers information about the epidemiology of resistance mechanisms, regular audits in specific patient populations are warranted to determine the frequency of azole resistance among different risk groups. These audits will enable clinicians to determine whether reassessment of azole monotherapy as a primary treatment option is necessary. Given the low and variable rates of positive cultures, culture-negative patients should also be included in azole-resistance surveillance programs.

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